II. Rejections under 35 U.S.C. §112, first paragraph, enablement

Claims 1-3, 5-11, 23-27, and 33-35 are rejected as allegedly containing subject matter that was not described in the specification in a way to enable one of skill in the art to make and use the invention. To the extent the rejection applies to the currently pending claims, Applicants respectfully traverse the rejection.

The Office Action specifically alleges that insufficient examples and guidance are provided to allow those of skill in the art to identify a catalytic domain of a glycosyltransferase and a catalytic domain of an accessory enzyme. The Office Action also alleges that a protein comprising only a catalytic domain would not necessarily have enzymatic function. Applicants respectfully traverse and point out that catalytic domain is defined in the specification at page 5, lines10-15 to be portion of an enzyme that is sufficient to carry out an enzymatic reaction. Thus, a catalytic domain is necessarily an active form of a glycosyltransferase or accessory enzyme.

In addition, Applicants respectfully point out that eukaryotic glycosyltransferases typically have amino terminal domains that are not required for enzymatic activity, but rather are used to direct the protein through a membrane and into an appropriate cellular compartment. (Specification at page 12, lines 18-27.) The "cytoplasmic domain," "signal-anchor domain," and "stem region" can be identified by those of skill in the art on the basis of homology to known glycosyltransferases. In addition, prokaryotic glycosyltransferases have amino terminal domains that span a membrane in the native protein that can be omitted form a fusion protein if desired by the user. (Specification at page 15, lines 22-24.) Thus, Applicants provide sufficient examples and guidance for use of catalytic domains in the practice of the claimed invention.

The Office Action also alleges that the specification does not provide enablement for a fusion protein comprising any glycosyltransferase and any accessory enzyme and that undue experimentation would be required to practice the full scope of the claimed invention. Applicants respectfully traverse the rejections. The Office Action does acknowledge that the specification is enabling for claims directed to a

polynucleotide that encodes a fusion protein comprising a specifically identified glycosyltransferase and a specifically identified accessory enzyme. (Office Action at page 4.) Applicants have added new claims 37-48 directed to the elected species (*e.g.*, a fusion protein comprising a sialyltransferase and a CMP-sialic acid synthetase). Thus, at the very least, the specification enables the new claims.

The Office Action appears to have focused improperly on inoperative embodiments, leading to the conclusion that undue experimentation would be required to practice the methods of the claimed invention. However, the proper test of enablement is "whether one skilled in the art could make or use the claimed invention from the disclosure in the patent coupled with information known in the art without undue experimentation" (*see, e.g.*, MPEP §2164.01). Claims reading on inoperative embodiments are enabled if the skilled artisan understands how to avoid inoperative embodiments. (*See, In re Cook and Merigold*, 169 USPQ 299, 301 (C.C.P.A. 1971)). In the present application, one of skill would know how to avoid inoperative embodiments and make the claimed fusion proteins without undue experimentation. Moreover, the present application provides guidance in the form of assays and working examples for making and identifying enzymatically active fusion protein.

Methods to construct nucleic acids that encode fusion proteins and to express those proteins in suitable cells are found in the specification at pages 27-36. Methods to detect activity of an accessory enzyme and a glycosyltransferase are known to those of skill in the art. Even if a user inadvertently constructs an inactive fusion protein, the user will be able to identify it and construct another embodiment of the claimed invention using the teachings of the specification. Specific methods for construction of a *Neisseria* CMP-Neu5Ac synthetase/α-2,3-sialyltransferase fusion protein are found in Example 1, beginning at page 38. The exemplified cloning methods can be extrapolated by those of skill to construct a desired fusion protein from known components. Assays for demonstrating the synthesis of desired oligosaccharides are taught at page 24, lines 21-31. Assays for a CMP-Neu5Ac synthetase/α-2,3-sialyltransferase fusion protein are found in Example 1.

The Examiner alleges that undue experimentation is required to practice the claimed invention, and that the fused form of the enzymes should be "kinetically favorable" with each other depending on the "turnover rate" of each enzyme. The Office Action also alleges that it would be unduly burdensome for one of skill in the art to form a "perfectly matched" pair of glycosyltransferase and accessory enzyme for a fusion protein. (Office Action at page 6.) Applicants assert that they have complied with the requirement for utility of the claimed fusion proteins and that no requirement for perfection is found in United States patent law.

In addition, other examples of the claimed invention, (*e.g.*, glycosyltransferase/accessory enzyme fusion proteins), have been reported. The application as filed includes detailed description of a UDP-glucose 4' epimerase fused to a β-1,4-galactosyltrasferase. (Example 2, specification at pages 49-52.) A post-filing publication describes construction of a eukaryotic α galactosyltransferase fused to an UDP-Glc/Gal eipmerase. (Chen *et al.*, J. Biol. Chem. 275:31594-31600 (2000)). The components of this fusion are disclosed in the specification at page 13, line 31; and page 19, lines 15-17. Chen *et al.* constructed their fusion protein by amplifying a known glycosyltransferase gene and a known accessory enzyme as is described and exemplified in the application. Clearly, those of skill in the art are able to choose appropriate partners for a fusion protein comprising a glycosyltransferase and an accessory enzyme, and to construct a polynucleotide encoding an active fusion protein with "practical advantages" as suggested by the Office Action.

In view of the above amendments and remarks, Applicants respectfully request that the rejections under 35 U.S.C. §112, first paragraph for alleged lack of enablement be withdrawn.

III. Rejections under 35 U.S.C. §112, first paragraph, written description

Claims 1-3, 5-11, 23-27, and 33-35 are rejected as allegedly containing subject matter that was not described in the specification in a way to that Applicants had possession of the claimed genus at the time of filing. The Office Action alleges that the

application does not provide any disclosure of structure for the DNA sequences encompassed by the claims. In addition, the Office Action alleges that the claimed genus is not adequately described. To the extent the rejection applies to the currently pending claims, Applicants respectfully traverse the rejection.

The invention is a genus of fusions proteins comprising a glycosyltransferase enzyme linked in frame to an accessory enzyme that synthesizes a sugar or sugar nucleotide that is a substrate for the glycosyltransferase. Applicants have elected the species comprising a sialyltransferase and a CMP-sialic acid synthetase. The claimed fusion proteins are useful for synthesizing oligosaccharides, particularly on a large scale. Previously, synthesis of oligosaccharides had been hampered by the need for expensive starting materials, *e.g.*, sugar nucleotides. Applicants were the first to discover that by fusing a known gene that encodes a glycosyltransferase to a second known gene that encodes an appropriate accessory enzyme, less expensive starting materials can be used to synthesize oligosaccharides. In addition, the efficiency of oligosaccharide synthesis is enhanced by use of the fusion proteins of the invention. The example of the elected species demonstrates cost-effective production of sialyllactose using a CMP-Neu5Ac synthetase/α-2,3-sialyltransferase fusion protein. Applicants emphasize that, the invention is in manipulation of known genes, not in isolation of novel genes from natural sources.

With regard to the structure of the claimed invention, the Examiner is apparently referring to *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997). "A description of a genus. . . may be achieved by means of . . . a recitation of structural features common to the members of the genus . . . ." *Lilly*, 43 USPQ2d at 1406.

Applicants respectfully remind the Examiner *Lilly* is properly limited to the facts of the case and that expansion of the holding of the case is improper. In Lilly the Federal Circuit ruled that isolation of a novel DNA sequence from nature (*e.g.*, from a particular organism) is not sufficient to provide description of related, but not yet isolated

DNA sequences from nature (*e.g.* from other organisms). In contrast, Applicants claim novel combinations of known DNA sequences.

The Examiner alleges that the specification does not disclose the structure of the DNA sequences encompassed by the claimed species. Applicants respectfully disagree. At the time of filing, the structure (*e.g.*, nucleotide sequences and encoded amino acid sequences) of many glycosyltransferases and accessory enzymes were known to those of skill in the art. Glycosyltransferases, including sialyltransferases, have recognizable structures that are well-known to those of skill. For example, eukaryotic glycosyltransferases have recognizable catalytic domains, "cytoplasmic domains," "signal-anchor domains," and "stem regions." (Specification at page 12, lines 18-27.) Similarly prokaryotic glycosyltransferases have amino terminal membrane-spanning domains and catalytic domains. (Specification at page 15, lines 22-24.) Amino acid and nucleic acid sequences are conserved among glycosyltransferases with similar enzymatic activities. Thus, the structure of known glycosyltransferases can be used by those of skill to identify similar enzymes on the basis of sequence homology. Many sialyltransferases have been cloned and their structure can be used to identify additional sialyltransferases based on homology to either known DNA sequences or encoded amino acid sequences. Applicants provide references for the structures of many glycosyltransferases and accessory enzymes that can be used by those of skill in the art to practice the invention. For the elected species, references for CMP-sialic acid synthetase genes, some including accession numbers, are found at page 22, line 31 through page 23, line 6 and in Example 1. References for eukaryotic sialyltransferases are found at page 14, lines 14-28. References for prokaryotic sialyltransferases are found at page 17, lines 3-8. The structures of CMP-Neu5Ac synthetase and α-2,3-sialyltransferase enzymes were known and described at the time of filing; therefore the structure of the elected species of fusion protein is adequately described by the specification.

For known DNA sequences, a reference to a public sequence disclosure is sufficiently descriptive. According to both the USPTO and the Federal Circuit Court of Appeals, information that is well known in the art need not be described in detail in the

specification. (MPEP 2163(II)(A)(2) and *Hybritech v. Monoclonal Antibodies,* 802 F.2d 1367 1379-80 (Fed. Cir. 1986)). Those of skill in the art recognize how to access the structure of isolated DNA sequences, (*e.g.*, by identifying such sequences in published references or in publicly accessible data bases, such as GenBank) and how to manipulate those DNA sequences in standard cloning procedures. Thus, the component structures of the claimed invention are adequately described, as are the methods to combine the components into a functional fusion protein.

The Office Action also alleges that the application does not provide adequate written description for the claimed genus and that a representative number of species within the genus is not found in the disclosure. Applicants respectfully traverse the rejection. As pointed out by the Examiner, the written description requirement for a claimed genus is "satisfied through sufficient description of a representative number of species ... by disclosure of relevant identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus." (Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1, "Written Description" Requirement, 66 Fed. Reg. 1106 (2001)). The identifying characteristics must distinguish the claimed invention from other materials; leading those of skill to the conclusion that the inventor was in possession of the claimed invention. *Id.* For biomolecules, relevant identifying characteristics include enzymatic activities. *Id.* at Fn. 42.

Here, Applicants provide both structural description and functional description for the claimed invention. The Application contains numerous references to sequences of glycosyltransferases and of accessory enzymes. These references provide the required structural disclosure. The Application also provides information about the enzymatic activity of the fusion proteins encoded by the claimed genus of DNA sequences, *e.g.* relevant identifying characteristics. Each encoded fusion protein molecule has two distinct enzymatic activities: that of a glycosyltransferase and that of an

accessory enzyme. In the case of the elected species, the encoded fusion protein has CMP-Neu5Ac synthetase activity and α-2,3-sialyltransferase. This embodiment is described, for example, at page 22, lines 29-31. ("These fusion proteins include a catalytic domain from a sialyltransferase and a catalytic domain from a CMP-sialic acid synthetase...") Those of skill would be able to distinguish the novel fusion proteins exhibiting two different, claimed activities from other materials.

With respect to the written description requirement for a claimed genus, description of a representative number of species does not require such specificity that support is provided for each species embraced by the genus. (MPEP 2163 – (II)(A)(3)(a)(ii)). Applicants have provided sufficient description of the elected species. As described above, Applicants have provided examples and description of combinations of sialyltransferases and CMP-sialic acid synthetases and the nucleic acid components that encode the sialyltransferases and CMP-sialic acid synthetase. Thus, Applicants have provided a representative number of species and have adequately described the claimed genus.

The Office Action also alleges that specific nucleotide sequences are required to provide descriptive support for the claimed invention. Applicants respectfully traverse. The process of the invention is found in the Examples. In Example 1, a gene encoding *Neisseria* CMP-Neu5Ac synthetase is fused to a gene encoding *Neisseria* α-2,3-sialyltransferase to make a fusion protein comprising the encoded products. Applicants disclose PCR primers to amplify the component genes and the source of the template, *e.g.*, reference for the sequence of the amplified gene. Using the primers and templates disclosed by Applicants, only one fusion product is possible and is thus described. Therefore, the example does provide a specific structure for a nucleic acid that encodes a fusion protein of the elected species. Using the examples, and standard molecular biology techniques taught in the specification, the application describes many more fusion proteins encoded by the claimed nucleic acids. Thus, those of skill in the art will be able use the described techniques to make and use the claimed invention.

In view of the above amendments and remarks, Applicants respectfully request that the rejections under 35 U.S.C. §112, first paragraph for alleged lack of written description be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at 415-576-0200.

Respectfully submitted,

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